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Does the Interval between Papanicolaou Tests Influence the Quality of Cytology?

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BACKGROUND. It is commonly believed that the sensitivity of Papanicolaou (Pap) tests decreases with a short interval between cytology samplings. To the authors' knowledge, there is only limited evidence to support this belief.

METHODS. For 5055 women in the Atypical Squamous Cells of Undetermined Significance (ASCUS)–Low Grade Squamous Intraepithelial Lesion (LSIL) Triage Study (ALTS), the Pap interval was defined as the number of days between the referral Pap smear demonstrating ASCUS or LSIL ("first cytology") and the enrollment liquid-based ("repeat") cytology. The authors investigated the influence of the interval between Pap smears on repeat cytology by examining percentages of abnormal findings, cellularity, and test sensitivity among women diagnosed with histologic grade 3 cervical intraepithelial neoplasia (CIN3) during the 2-year course of the ALTS. In addition, because human papillomavirus (HPV) DNA adjunct testing is now performed, the authors evaluated HPV viral load, which was assayed using residual liquid cytology specimens, in women with CIN3.

RESULTS. The Pap interval ranged from 8–30 days in 763 women, 31–60 days in 2317 women, 61–90 days in 1090 women, 91–120 days in 491 women, and 121–184 days in 394 women (mean of 61.3 days; standard deviation of 34 days). Repeat cytologic interpretations of unsatisfactory findings, ASCUS, and high-grade squamous intraepithelial lesion (HSIL) did not appear to vary among the Pap interval groups. However, low-grade cytologic regression occurred with an increasing Pap interval; negative cytology increased from 28.3% (8–30 days) to 41.6% (121–184 days) ($P < 0.0001$) whereas LSIL cytology decreased (P trend = 0.002).

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The approximate cellularity of the samples was slightly better in the interval group of 8–30 days (P Trend = 0.04). Among women with CIN3, the repeat test sensitivity at a threshold of ASCUS or greater and the HPV DNA viral load was not found to vary by Pap interval (P Trend = 0.80 and P Trend = 0.36, respectively).

CONCLUSIONS. The authors concluded that a short Pap interval (range, 15–120 days) does not significantly affect the quality of liquid-based repeat cytology, nor the viral load tested from a residual liquid-based specimen. ***Cancer (Cancer Cytopathol)* 2005;105:133–8.** *Published 2005 by the American Cancer Society*.*

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The Papanicolaou (Pap) test for cervical carcinoma screening involves gently scraping the ectocervix and endocervical os to remove epithelial cells for cytologic evaluation. When the results of an initial Pap test necessitate a repeat sample, expert opinion has dictated that a repeat specimen should not be obtained until 2–3 months later; otherwise, the test sensitivity will be compromised.[1,2]

The rationale for delayed repeat sampling after the initial Pap test is the belief that it may take several months for abnormal epithelium to regenerate and yield abnormal cells in the repeat cytology.[3] Evidence for decreased Pap test sensitivity with short intervals between cytology samplings came primarily from studies of women whose initial cytologic findings prompted colposcopy.[4–7] Although it was not clear in all the studies whether the outcome was any cervical intraepithelial neoplasia (CIN) or was limited to high-grade CIN and carcinoma, repeat Pap tests at the time of colposcopy demonstrated sensitivities ranging from 25–57%, which was lower than presumed.

To our knowledge, there has been little rigorous examination to date of the influence of time between Pap tests on sensitivity among large groups of women measured longitudinally. Consequently, we examined the impact of the time interval to repeat cytologic sampling within the Atypical Squamous Cells of Undetermined Significance (ASCUS)–Low Grade Squamous Intraepithelial Lesion (LSIL) Triage Study (ALTS), a multicenter randomized clinical trial designed to compare management strategies for women with equivocal and low-grade cytologic results.

MATERIALS AND METHODS

The ALTS was a multicenter randomized clinical trial that evaluated three management strategies for women with ASCUS or LSIL cytology: immediate colposcopy, human papillomavirus (HPV) triage, and conservative management based on repeated cytology. The design, methods, and primary results of the ALTS have been described previously.[8–10] Briefly, women eligible for ALTS were referred to the trial with cytologic findings of ASCUS or LSIL obtained at a community health center; 3488 women with ASCUS and 1572 women with LSIL were enrolled into ALTS.

Once enrolled, women were randomly assigned to one of the three management strategies. Regardless of the assigned study arm, all women underwent a pelvic examination at the time of enrollment. A cervical specimen was collected with a Papette® broom (Wallach Surgical, Orange, CT) and rinsed directly into a PreservCyt® vial (Cytyc Corporation, Boxborough, MA) for ThinPrep® cytology (Cytyc Corporation) and subsequent HPV DNA testing with Hybrid Capture® 2 (HC2; Digene Corporation, Gaithersburg, MD). A second cervical sample was obtained at the time of enrollment with a Dacron® swab (Technical Service Consultants Ltd, Heywood, Lancashire, UK) for HPV DNA typing; this sample was not considered for the current analysis.

Specimens were processed using a semiautomated ThinPrep 2000 Processor (Cytyc Corporation). In this process, samples are mixed thoroughly, breaking up mucus, blood, and other nondiagnostic debris. Negative pressure pulses then "sip" the specimen through a filter with small pores. As cellular material (which cannot pass through the pores) collects on the filter, resistance increases until it equals the suction negative pressure, at which point the sipping stops. As a general rule, the lower the cellularity of the sample, the higher the volume that is "sipped" through the filter. Material collected on the filter is then transferred to a glass slide to make a ThinPrep slide.

Thin Prep slides were screened at each clinical center by a cytotechnologist and evaluated by a cytopathologist. The results were reported according to the Bethesda system, with distinction made between high-grade squamous intraepithelial lesions(HSILs)-grade 2 CIN (CIN2) and HSIL-CIN3.

After the ThinPrep slide was prepared, a 4-mL sample from the same PreservCyt vial was used for the HC2 test to detect oncogenic HPV types (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, and -68). A threshold of 1 picogram (pg) of HPV DNA per mL of

solution was considered to be positive. The result was considered as missing when there was not adequate (< 4 mL) sample remaining in the vial after preparation of the ThinPrep slide.

For this analysis, we considered the Pap interval to be the number of days between the date of the referral Pap smear and the date of the cytology specimen obtained at the time of enrollment. For the remainder of the article, we will refer to the community referral Pap smear as "first cytology" and the enrollment liquid-based ThinPrep specimen as "repeat cytology." We excluded from this analysis five women for whom no repeat cytology information was available. We grouped the Pap intervals into 5 clinically intuitive categories: range of 8–30 days, range of 31–60 days, range of 61–90 days, range of 91–120 days, and range of 121–184 days. Alternative categories (e.g., quartiles) did not alter the conclusions. Viral load, as measured by the HC2 test (relative light units normalized to 1 pg/mL HPV-16-positive controls [RLU/PC]), was grouped into 3 categories: < 1 RLU/PC, (negative) 1–100 RLU/PC, and > 100 RLU/PC. Endpoint case definitions were based on cumulative Pathology Quality Control (QC) group histologic diagnoses of CIN3 or carcinoma over the 2-year span of the trial. For statistical analysis, we used standard contingency table methods for categorical variables and linear regression for "sip volume," a continuous variable. We used Stata 8.0 analytic software (Stata Corporation LP, College Station, TX).

RESULTS

Pap intervals in the 5055 women in the current study ranged from 8–184 days, with a mean of 61.3 days (standard deviation [SD] of 34 days) and a median of 52 days. The interval was 8–30 days in 763 women, 31–60 days in 2317 women, 61–90 days in 1090 women, 91–120 days in 491 women, and 121–184 days in 394 women. Of the 763 women with the shortest interval of 8–30 days, only 33 underwent repeat sampling within 8–14 days after the community Pap smear; therefore, our results for the group with a Pap interval of 8–30 days are based mainly on data from women with a Pap interval of 15–30 days. In the longest interval of 121–184 days, the 394 observations were well distributed throughout the period.

Table 1 shows the relation between repeat cytology interpretation and Pap interval. Although the percentage of unsatisfactory cytology findings was slightly higher for the group in which the sample was taken within 30 days after the referral cytology, the difference was not statistically significant ($P = 0.11$). Among the satisfactory Pap interpretations, the percentage of negative cytology gradually increased from 28.3% for the samples taken within 30 days after the referral cytology to 41.6% for the samples taken after 120 days; the chi-square test for trend was found to be highly significant (P Trend < 0.0001). When stratified by ThinPrep diagnosis, the percentage of slides interpreted as ASCUS, HSIL-CIN2, and HSIL-CIN3+ did not appear to vary by Pap interval, but the percentage of LSIL cytology decreased from 30.3% in the Pap interval ≤ 30 days to 20.3% in the interval > 120 days (P trend = 0.002, goodness-of-fit chi-square test). When the analysis was stratified by age (data not shown), the decline in LSIL with time and the corresponding increase in normal results were strongly evident in the group of women age < 30 years. In women age ≥ 30 years, there was a lower prevalence of LSIL and the trend was weaker.

The volume of samples used for preparing the ThinPrep slides in each of the Pap interval groups is shown in Figure 1. As mentioned, this volume is inversely correlated with cellularity; generally, the lower the cellularity of the sample, the higher the volume needed to prepare the slide. The mean volume used was 4.6 mL (SD of 3.7 mL) for Pap intervals of 8–30 days, 4.8 mL (SD of 3.7 mL) for Pap intervals of 31–60 days, 4.9 mL (SD of 3.7 mL) for Pap intervals of 61–90 days, 4.9 mL (SD of 3.5 mL) for Pap intervals of 91–120 days, and 5.0 mL (SD of 4.0 mL) for Pap intervals of 121–184 days. These results suggest that the cellularity of the samples was slightly better when the ThinPrep sample was taken within the first 30 days after the referral Pap smear, but the difference was not statistically significant ($P = 0.098$).

To evaluate the sensitivity of the repeat specimen, Table 2 shows the cytology interpretations from women with a final QC histologic diagnosis of CIN3 or carcinoma. The percentage of negative cytology (false-negative result) was similar across the Pap interval groups (P trend = 0.80). The percentage of ASCUS cytology was slightly higher in the group with a Pap interval of 8–30 days compared with the other groups. The percentage of LSIL cytology was variable among the interval groups. The percentage of HSIL cytology varied from 32.7% in the group with a Pap interval of 8–30 days to 33.6%, 41.9%, 34.6%, and 42.5% in the other Pap interval groups, but this difference was not statistically significant (P trend = 0.22).

Finally, as another measure of specimen adequacy, we evaluated the relationship between the Pap interval and viral load assayed from the residual liquid-based specimen in patients with a final QC histologic diagnosis of CIN3 (Table 3). HPV testing was highly sensitive for the detection of prevalent and incipient CIN3; there were relatively few negative values (< 1 pg/mL). We found that the viral load was not

TABLE 1
Repeat Cytology Interpretation by Pap Time Interval in All Women

Repeat cytology interpretation	No. of days between referral cytology and enrollment cytology No. (%)					
	8–30	31–60	61–90	91–120	121–184	Total
Unsatisfactory	10 (1.3)	23 (1.0)	9 (0.8)	3 (0.6)	2 (0.5)	47 (0.9)
Negative	216 (28.3)	788 (34.0)	382 (35.1)	185 (37.7)	164 (41.6)	1735 (34.3)
ASCUS	234 (30.7)	676 (29.2)	308 (28.3)	153 (31.2)	118 (30.0)	1489 (29.5)
LSIL	231 (30.3)	639 (27.6)	287 (26.3)	103 (21.0)	80 (20.3)	1,340 (26.5)
HSIL—CIN2	59 (7.7)	172 (7.4)	88 (8.1)	39 (7.9)	25 (6.3)	383 (7.6)
HSIL—CIN3+	13 (1.7)	19 (0.8)	16 (1.5)	8 (1.6)	5 (1.3)	61 (1.2)
Total	763 (100.0)	2317 (100.0)	1090 (100.0)	491 (100.0)	394 (100.0)	5055 (100.0)

Pap: Papanicolaou smear; ASCUS: atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; CIN2: Grade 2 cervical intraepithelial neoplasia; CIN3: Grade 3 cervical intraepithelial neoplasia.
Severity of results by time interval, P trend < 0.001, chi-square test.
Unsatisfactory results versus satisfactory results, P trend $= 0.11$.
Negative results versus abnormal results, P trend < 0.0001.
Goodness-of-fit chi-square result for low-grade squamous intraepithelial lesion. P trend $= 0.002$.

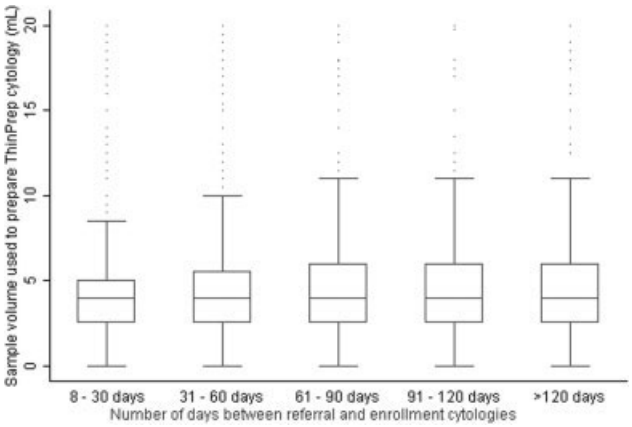

FIGURE 1. Mean volume of the liquid-based sample used to prepare the ThinPrep slide (sip volume) by time interval to repeat cytology; an approximation of sample cellularity is shown ($n = 5033$). The Spearman rho was 0.0294. There was no significant linear relationship between the sip volume and time interval ($P = 0.098$).

statistically significantly different among the different Pap interval groups (P trend $= 0.76$).

DISCUSSION

The controversy regarding the adequacy of a repeat cytology taken soon after a previous Pap smear gained momentum with the publication of several articles related to the false-negative rate of Pap smears obtained at the time of colposcopy for the follow-up of an abnormal result on the first Pap smear.[4–6] The majority of these studies compared the calculated sensitivity of the second sample, in which patients had colposcopic follow-up, against the presumed sensitivity of the first (referral) Pap smear.

Based on the comparison of the presumed sensitivity of the first cytology and the calculated sensitivity of the repeat cytology taken at colposcopy, the conclusion was reached that cytology samples taken too soon after a previous Pap smear had a lowered sensitivity. The main hypothesis to explain this poor sensitivity was that the first Pap smear scraped the lesion so that there were not enough abnormal cells remaining at the time of the repeat sampling.

To our knowledge, one of the most detailed studies focusing on the performance of the repeat cytology was performed by Bishop et al.[1] They evaluated 278 repeat Pap smears with intervals ranging from 4–539 days and concluded that there is a lack of sensitivity when the cytology is repeated at close intervals ($<$ 120 days). This small study considered as a case any patient with a biopsy result that demonstrated "abnormality," thereby introducing vagueness into the reference standard of disease.

We evaluated four lines of evidence to assess specimen quality by time interval: 1) percentage of abnormal findings, 2) sensitivity for histologic CIN3, 3) cellularity of the sample, and 4) HPV viral load among women found to have CIN3.

When we evaluated the results in the total ALTS population, we found that the percentage of negative cytology increased over time, from 28.3% in the group with the shortest Pap interval to 41.6% in the group with the longest Pap interval, a difference that was statistically significant. In a parallel vein, we found a decreasing percentage of LSIL cytologic interpretations with an increasing Pap interval in women age $<$ 30 years. We propose that the longer interval allowed time for the clearance of transient HPV infections and

TABLE 2
Repeat Cytology Interpretation by Pap Time Interval in Women with CIN3/Carcinoma Histology

Repeat cytology interpretation	No of days between referral cytology and enrollment cytology No. (%)					
	8–30	31–60	61–90	90–120	121–184	Total
Unsatisfactory	2 (2.0)	1 (0.4)	-	-	-	3 (0.6)
Negative	12 (11.9)	35 (15.1)	12 (10.3)	7 (13.5)	7 (17.5)	73 (13.5)
ASCUS	26 (25.7)	46 (19.8)	22 (18.8)	12 (23.1)	6 (15.0)	112 (20.7)
LSIL	28 (27.7)	72 (31.0)	34 (29.1)	15 (28.8)	10 (25.0)	159 (29.3)
HSIL	33 (32.7)	78 (33.6)	49 (41.9)	18 (34.6)	17 (42.5)	195 (36.0)
Total	101 (100.0)	232 (100.0)	117 (100.0)	52 (100.0)	40 (100.0)	542 (100.0)

Pap: Papanicolaou smear; CIN3: Grade 3 cervical intraepithelial neoplasia; ASCUS: atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion.
Severity of results by time interval, P trend = 0.85, chi-square test.
Analysis for trend, negative results versus abnormal results, $P = 0.80$.
Analysis for trend, high-grade squamous intraepithelial lesion (HSIL) versus < HSIL, $P = 0.22$.

TABLE 3
Viral Load by Pap Time Interval in Women with CIN3/Carcinoma Histology

Viral load[a]	No. of days between referral cytology and enrollment cytology/HPV DNA test No. (%)				
	8–30	31–60	61–90	91–184	Total
< 1	6 (6.4)	16 (7.1)	6 (5.4)	5 (5.8)	33 (6.4)
1–100	32 (34.0)	75 (33.2)	46 (41.1)	36 (41.4)	189 (36.4)
> 100	56 (59.6)	135 (59.7)	60 (53.6)	46 (52.9)	297 (57.2)
Total	94 (100.0)	226 (100.0)	112 (100.0)	87 (100.0)	519 (100.0)

Pap: Papanicolaou smear; CIN3: Grade 3 cervical intraepithelial neoplasia; HPV: human papillomavirus ASCUS: atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion.
[a] Relative light units normalized to 1 pg/mL human papillovirus 16-positive controls [(RLU/PC)] using Hybrid Capture 2 testing.
For women with positive hybrid capture 2 tests (≥0.8 RLU/PC), Spearman rho = −0.0418; (n = 489); ($P = 0.3561$).
Chi square test, P trend = 0.76.

therefore for LSIL to revert to negative on later repeat cytology. This could be considered clinically advantageous given the benign course of most HPV infections and the low-grade lesions caused by HPV.

The most important measure of the quality of a cytology specimen is its sensitivity for appropriately referring women with histologic CIN3 for evaluation. Previously published literature has reported a reduced sensitivity for early repeat Pap smears obtained at colposcopy compared with the hypothetical sensitivity of the initial referral Pap smear. Rather than comparing the sensitivities of "first" and "repeat" cytology, we performed an internal comparison of time intervals and the sensitivity of the repeat cytology within the context of a clinical trial with uniform sampling methodology and follow-up for disease ascertainment. This analysis showed that the sensitivity and false-negative rate of the repeat (enrollment) liquid-based cytology for CIN3 did not vary by time interval.

The results of the current study also demonstrate that cellularity (as approximated by sip volume) was not adversely affected by a short Pap interval. In addition, cervical cytologic specimens are being used increasingly for adjunctive HPV DNA testing. Therefore, as another measure of adequate lesion sampling, we evaluated HPV viral load by time sampling intervals (Table 3). To exclude unimportant, transient HPV infections, we focused on women with a final QC histologic diagnosis of CIN3/carcinoma. The statistical analysis did not demonstrate any significant difference among the various Pap interval groups.

The strengths of the current analysis, which is based on ALTS data, are the large numbers of repeat cytology samples (n = 5055) obtained with uniform methodology and the virtually complete ascertainment of disease, defined as histologic CIN3 (n = 535 cases) or carcinoma (n = 7 cases) diagnosed within

2 years of enrollment. However, a limitation of the ALTS data is that the repeat cytology was exclusively liquid based and therefore these findings may not be generalizable to repeat conventional Pap smears.

A short Pap interval does not appear to affect the quality of a repeat liquid-based cytology or the HPV viral load. However, a short repeat interval may be correlated with a higher probability of detecting transient LSIL changes in younger women and consequently a higher referral to colposcopy.

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